discloses data that the claimed conjugates do elicit antibodies that are protective against bacterial infection, at Tables 5-7, Opsonophagocytic assays (OP) and Serum bactericidal assays (SBA). The addition to claim 1 of the element "wherein the protein is a bacterial protein or a synthetic protein containing lysine or cysteine residues", and to claim 16 of the element "wherein the protein is a bacterial protein or a synthetic protein containing lysine or cysteine residues", is supported at page 9, lines21-25.

Claims 4 and 39 have been amended by deleting "Haemophilus", and thus these amendments do not introduce new matter. Claim 15 has been amended so that claim 15 now depends upon claim 1. Additional claims 59 and 60 are dependent upon claims 1 and 16 respectively. These claims encompass the limitation that the polysaccharide or oligosaccharide components of the claimed conjugates are at least 95% acryloylated. This limitation is supported in the specification at page 9, lines 6-7: "The resulting N-acryloylated polysaccharide or N-acryloylated oligosaccharide is at least about 95% acryloylated or greater." Additional claims 61 and 62 are also dependent upon claims 1 and 16 respectively. New claims 61 and 62 introduce the limitation that the saccharide components of the conjugates are at least 50% de-N-acetylated. These limitations: "and wherein at least 50% of the N-propionated saccharides are de-N-acetylated" (claim 61), and "wherein the polysaccharide or oligosaccharide is at least 50% de-N-acetylated" (claim 62), are supported at page 6, line 13. Lastly, new claim 63 is supported at page 9, lines 21-25. Neither the amendments nor the additional claims introduce new matter. Entry of these amendments and new claims is respectfully requested.

Supplemental Response to Section 112, First Paragraph Rejection, (Examiner's Action #9 of Official Action mailed January 28, 2002):

Claims 25 and 40 have been rejected under 35 U.S.C. §112, first paragraph, because the Examiner contends that the specification does not enable a pharmaceutical composition or vaccine comprising more than one vaccine component. In particular, the Examiner argues that there is no showing by the specification that combination vaccines comprising an N-propionated polysaccharide or oligosaccharide protein-conjugate would effectively elicit an "optimal" immune response.

Regarding the Examiner's suggestion that immune responses be "optimal", there is no requirement in the patent statute that inventions be "optimal", they need only be "useful".

Accordingly, applicants need only to provide a disclosure that enables one skilled in the art to make and use the claimed invention. For the reasons discussed below, the application provides sufficient information to lead one skilled in the art to expect to make and use mutlivalent vaccines without undue experimentation.

The Examiner relies upon two references, Barrington *et al.* (*Infect. Immun.* 61:432-438, 1993) and Corbel (*Biologicals* 22:353-360, 1994) to support her contention that the art reports "potential interference by one or more added vaccine components and suppression of antibody response to the polysaccharide or the carrier protein". Therefore the Examiner argues that undue experimentation would be required by one of ordinary skill in the art to practice the invention as claimed in claims 25 and 40. The Examiner also asserts that combination vaccines may lead to epitope suppression of anti-polysaccharide responses and therefore claims 25 and 40 would require undue experimentation to practice the invention as claimed. Applicants respectfully disagree with the grounds of this rejection.

The Examiner's contention that epitope suppression in combination vaccines provides a basis for an enablement rejection is improper. Applicants respectfully point out that epitope suppression in combination vaccines is an inconsistent phenomenon which does not prohibit the use or development of combination vaccines. Corbel, cited by the Examiner, even admits that epitope suppression is a concern that may only be determined by examining the effects of a combination vaccine already in use: "Some of the potential problems, such as sub-optimal antibody responses through antigenic competition or epitope suppression[11], may not be evident from laboratory tests but will only be detected by careful monitoring of vaccinees. Certain of these effects may themselves be dose- or schedule-dependent[12] and thus amenable to management." (Corbel, last paragraph, page 359, to first paragraph page 360). Therefore, a rejection of undue experimentation based on a concern of epitope suppression is improper, as the above quote reports that testing for epitope suppression should occur by monitoring combination vaccines *in use*, and that epitope suppression may therefore be managed. Such optimization methods routine in the art for optimizing vaccine dosing, although desirable, does not support a finding that the claimed inventions are not enabled.

Further, an enablement rejection for combination vaccines based on an argument that undue experimentation is required to determine whether non-epitope-specific suppression occurs is also improper. Barrington et al., also cited by the Examiner, does not suggest that non-

epitope-specific suppression is a prohibitive concern for combination vaccines. Barrington et al. state that non-epitope-specific suppression occurs in specific circumstances: "In conclusion, the data presented here show that suppression of antibody responses in human adults can occur when a protein antigen is given prior to its use as a carrier in a polysaccharide conjugate vaccine." (page 437, last paragraph). Barrington et al. state that non-epitope-specific suppression is not a common phenomenon for polysaccharide conjugates: "Non-epitope-specific suppression has not been consistently reported for haptenated proteins or polysaccharide conjugates..." (page 437, 1st column, 2nd full paragraph). Because Barrington et al. report that non-specific-epitope suppression may occur when protein antigens are used in pre-immunization, applicants assert that general guidance therefore exists in the art of combination vaccines such that one could avoid using the claimed combination vaccines in such a manner. Therefore, undue experimentation would not be required to practice the invention as claimed.

The above passages taken from the cited references indicate that epitope suppresion (both epitope-specific and non-epitope specific) is not a prohibitive concern in the development and use of combination vaccines. Seven years after these references were published, the art still does not consider epitope suppression to be a stumbling block for combination vaccines. The abstract from the article by N. Halsey ("Combination Vaccines: Defining and Addressing Current Safety Concerns", *Clinical Infectious Diseases,* (2001), 33(Suppl. 4):S312-8; copy enclosed), states: "Historical problems with vaccines, including intussus-ception after rotavirus vaccine, carrier supression with tetanus toxoid conjugate vaccines, and decreased immunogenicity of some *Haemophilus influenzae* type b conjugate vaccines when mixed with acellular pertussis-diphtheria-tetanus, have contributed to some misperceptions about current vaccines. *There is no evidence that adding additional vaccines through combination products increases the burden on the immune system, which has the capability of responding to many millions of antigens*" (emphasis added). Because the art does not consider epitope suppression to be a prohibitive concern for the use or development of combination vaccines, applicants assert that a rejection of undue experimentation based on the concern of epitope suppression is improper.

The specification does provide guidance as to how to determine whether vaccines can elicit the production of antibodies that would be protective, i.e., by opsonophagocytic and serum bactericidal assays. These assays will determine whether antibodies elicited by a

vaccination, including vaccinations with combined vaccines, are bactericidal and thus protective. Claims 25 and 40 are dependent claims that specify further elements for N-propionated polysaccharide/oligosacharide-protein conjugate combined vaccine and pharmaceutical compositions; and that the specification enables one skilled in the art to determine whether such compositions may elicit bactericidal antibodies.

In the Office Action mailed January 28, 2002, the Examiner states that the specification enables single conjugate component vaccines, "...the specification, while being enabling for a pharmaceutical composition or a vaccine comprising a non-combination, i.e., a single conjugate component vaccine, comprising an N-acryloylated polysaccharide or oligosaccharide conjugated to a protein as claimed..." (page 7, lines 4-6). As single conjugate component vaccines are patentable, applicants are therefore entitled to claim all uses disclosed, i.e. combination vaccines. (*In re Kuehl, 475 F.2d 658, 177 USPQ 250 (CCPA 1973)*) and (*In re Pleuddemann, 910 F.2d 823, 15 USPQ 2D 1738 (U.S. App. 1990)*). Also, from *Johnson & Johnston Associates Inc. v. R.E. Service Co., Inc. and Mark Frater, 285 F.3d 1046, 62 USPQ 2D 1225 (U.S. App. 2002),* applicants must claim all disclosed subject matter or risk an allegation that non-claimed subject matter is dedicated to the public. Based on their disclosure, applicants are entitled to claim combination or multivalent vaccines as disclosed and claimed by applicants. Thus, in considering: (1) that the Corbel reference reports epitope suppression is best determined through the *actual use* of combination vaccines, (2) that the Barrington et al. reference states that non-specific epitope suppression occurs with pre-immunization of protein antigens (and the present invention does not mandate that combination vaccines must be administered with a pre-immunization of protein antigens), (3) that the Halsey reference teaches there is no evidence that combination vaccines increase the burden on the immune system, and (4) the cited law above; a rejection based on undue experimentation is improper in view of both the art and the law. Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Supplemental Response to Section 102(b) Rejection, (Examiner's Action #15 of Official Action mailed January 28, 2002):

Claims 1-4, 8, 11-14, 16, 17 and 19-22 have been rejected under 35 U.S.C. §102(b) as being anticipated by Pon, R.A. (*The Study of Polysialic acid Conjugates.* Master's

Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992). The Examiner contends that Pon reports polysaccharide or oligosaccharide-protein conjugates produced by a method comprising de-N-acetylating saccharides using a de-N-acetylating base reagent, followed by N-acryloylating the de-N-acetylated saccharide with an acryloylating reagent, and directly conjugating the resultant saccharide to a protein. Although applicants have amended the claims in order to more distinctly claim the instant invention, applicants respectfully disagree with this rejection for the reasons stated below.

Pon does not provide any evidence that a 15% N-acryloylated colominic acid comprising conjugate, let alone any protein glycoconjugate produced by Michael-type additions, can elicit protective antibodies. Further, the conjugates described by Pon do not possess the same structural characteristics as the claimed conjugates, i.e. where the protein component of the conjugates are coupled to either bacterial proteins or synthetic proteins containing lysine or cysteine residues.

At section 4.2.3.3 "Protein glycoconjugates via Michael-type additions", Pon reports 4 different conjugates prepared by Michael-type addition. The first conjugate consists of 15% N-acryloylated colominic acid conjugated to BSA or to IgG: "The first model used to test the feasibility of conjugate addition of lysine was the coupling of 15% N-acryloylated colominic acid (4-13) to BSA (4-17) or to porcine IgG (4-36) (fig. 4-19)." (page 146, last paragraph). As the claimed conjugates comprise either bacterial or synthetic protein components, whereas Pon's "first model" conjugate comprises porcine or bovine protein components, Pon's first conjugate does not contain all of the elements of the claimed conjugates, and thus, does not anticipate the present invention.

The other three types of conjugates mentioned by Pon are described at page 149, lines 11-14: "Basically, the N-acryloylated derivatives 4-13, 4-14, and 4-15 were conjugated to BSA (4-17) or TT (4-31) in essentially the same manner using high amounts of Michael acceptor to protein (>100 eq) in concentrated solutions (20 mg protein/ml buffer)." The N-acryloylated derivatives 4-13, 4-14 and 4-15 are described at page 128, Figure 4.9. Figure 4.9 shows that these derivatives are not de-N-acetylated and re-N-acryloylated at de-N-acetylated termini, like the claimed conjugates. Therefore, as the N-acryloylated derivative conjugates do not possess all of the elements described in the conjugates of claim 1 or claim 16, these derivative conjugates do not anticipate the present invention.

Thus, as "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference", (*Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987), applicants respecfully request reconsideration and withdrawal of these grounds of rejection.

Supplemental Response to Section 103(a) Rejections, (Examiner's Actions #21 and #22 of the Official Action mailed January 28, 2002):

Claims 1 and 8-10 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Pon, R.A. (*The Study of Polysialic acid Conjugates.* Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992) in view of Blake *et al.* (U.S. Patent No. 5,439,808). The Examiner contends that the combination of Pon and Blake *et al.* makes obvious saccharide-protein conjugates, wherein the protein is a *N. meningitidis* outer membrane protein.

Claims 1, 16 and 22-24 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Pon, R.A. (*The Study of Polysialic acid Conjugates.* Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992) in view of Blake *et al.* (U.S. Patent No. 5,439,808). The Examiner contends that the combination of Pon and Blake *et al.* makes obvious pharmaceutical compositions comprising saccharide-protein conjugates and adjuvants.

Applicants respectfully disagree with these grounds of rejection because Pon does not teach or suggest all the claim limitations recited by claims 1 or 16. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 180 USPQ 580 (CCPA 1974). As stated previously, Pon reports the conjugation of N-acryloyl colominic acid to BSA or IgG, wherein the colominic acid has only been 14.8% de-N-acetylated. In contrast, claim 1 of the instant application recites "at least 50% of the N-propionated saccharides are de-N-acetylated", and claim 16 recites "wherein the polysaccharide or oligosaccharide is at least 50% de-N-acetylated". Further, Pon does not teach or suggest that 15% N-Acryloylated colominic acid conjugates can elicit the production of protective antibodies.

The other Pon conjugates produced by Michael-type addition (the N-acryloyl

derivative conjugates) also do not possess all of the claim limitations. Specifically, these derivative conjugates are not re-acryloylated at de-N-acetylated termini.

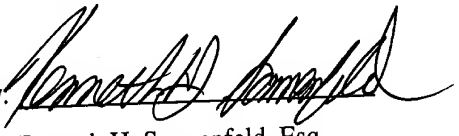
Therefore, as the primary motivation of the Examiner's combination fails to teach or suggest all of the limitations of claim 1, these 103(a) rejections are improper. Further, if an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Applicants respectfully request reconsideration and withdrawal of these grounds of rejection.

AUTHORIZATION

No additional fee is believed to be necessary. The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 13-4500, Order No. 3842-4043US1. A DUPLICATE COPY OF THIS PAGE IS ATTACHED.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

By: 

Kenneth H. Sonnenfeld, Esq.
Registration No. 33,285

Dated: June 17, 2002

CORRESPONDENCE ADDRESS:

MORGAN & FINNEGAN, L.L.P.
345 Park Avenue
New York, New York 10154
(212) 758-4800
(212) 751-6849 Facsimile

APPENDIX:

VERSION OF THE AMENDMENTS TO THE CLAIMS AND SPECIFICATION SHOWING DELETIONS AND ADDITIONS

IN THE CLAIMS:

Claims 1, 4, 15, 16, and 39 have been amended as follows:

1. A polysaccharide-protein conjugate or oligosaccharide-protein conjugate [that elicits protective antibodies wherein said conjugates comprise] comprising an N-propionated saccharide directly coupled to a protein at a β-position of a propionate moiety[,]; wherein the N-propionated saccharide directly coupled to the protein at the β-position of the propionate moiety elicits protective antibodies; wherein the N-propionated saccharide is de-N-acetylated and N-acryloylated at the de-N-acetylated terminus; and wherein the protein is a bacterial protein or a synthetic protein containing lysine or cysteine residues.

4. The conjugates according to claim 1 wherein the the saccharide is derived from a polysaccharide obtained from *Escherichia coli*, Meningococcus, Pneumococcus, Streptococcus, [Haemophilus,] Neisseria, Salmonella, Klebsiella, or Pseudomonas.

15. [A polysaccharide-protein conjugate or oligosaccharide-protein conjugate comprising an N-propionated] The conjugates according to claim 1 wherein the saccharide is derived from a polysaccharide obtained from group B *Streptococcus* type III [polysaccharide-tetanus toxoid conjugate], and wherein the protein is tetanus toxoid.

16. A polysaccharide-protein conjugate or oligosaccharide-protein conjugate that elicits protective antibodies produced by a method comprising:

A) de-N-acetylating an isolated polysaccharide or oligosaccharide using a de-N-acetylating reagent to form a de-N-acetylated polysaccharide or a de-N-acetylated oligosaccharide,

B) N-acryloylating the de-N-acetylated polysaccharide or the de-N-acetylated oligosaccharide at a de-N-acetylated terminus with an acryloylating reagent to form an N-propionated polysaccharide or an N-propionated oligosaccharide, and

C) directly coupling at a β-position of a propionate moiety of the N-propionated polysaccharide or the N-propionated oligosaccharide to a protein to form the polysaccharide-protein conjugate or the oligosaccharide protein conjugate; wherein the protein is a bacterial protein or a synthetic protein containing lysine or cysteine residues.

39. The vaccine according to claim 38 wherein the bacteria is selected from the group consisting of *Escherichia coli*, Meningococcus, Pneumococcus, Streptococcus, [Haemophilus,] Neisseria, Salmonella, Klebsiella, and Pseudomonas.